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JC868 U.S. PTO 09/27/00

JC541 U.S. PTO 09/671050 09/27/00

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53 (b))

Attorney Docket No.	LEX-0046-USA
First Inventor or Application Identifier	Gregory Donoho *et al.*
Title	Novel Human Kinase Proteins and Polynucleotides Encoding the Same
Express Mail label No.	EL584856677US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. ☐ *Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages 26] (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the disclosure
3. ☐ Drawing(s) (35 U.S.C.113) [Total Sheets]
4. Oath or Declaration [Total 1]
   - a. [X] Newly unexecuted (original or copy)
   - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 16 completed)
     - i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

*NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. §1.28).

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   - a. ☐ Computer Readable Copy
   - b. [X] Paper Copy (identical to computer copy)
   - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
9. ☐ English Translation Document *(if applicable)*
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
11. ☐ Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
13. [X] *Small Entity Statement(s (PTO/B/09-12) ☐ Statement filed in prior application, Status still proper and desired
14. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
15. ☐ Other: ....

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No:______

Prior application information: Examiner______ Group/Art Unit:______

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference.

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Name (Print/Type)	Lance K. Ishimoto	Registration No.	41866
Signature	*[signature]*	Date	Sept. 27, 2000

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STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(c)) -- SMALL BUSINESS CONCERN

Docket Number (Optional)
LEX-0046-USA

Applicant, Patentee, or Identifier: Gregory Donoho et al.
Application or Patent No.:
Filed or Issued: September 27, 2000
Title: Novel Human Kinase Proteins and Polynucleotides Encoding the Same

I hereby state that I am
☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN Lexicon Genetics Incorporated

ADDRESS OF SMALL BUSINESS CONCERN 4000 Research Forest Drive, The Woodlands, TX 77381

I hereby state that the above identified small business concern qualifies as a small business concern as defined in 13 CFR Part 121 for purposes of paying reduced fees to the United States Patent and Trademark Office. Questions related to size standards for a small business concern may be directed to: Small Business Administration, Size Standards Staff, 409 Third Street, SW, Washington, DC 20416.

I hereby state that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

☒ the specification filed herewith with title as listed above.
☐ the application identified above.
☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern, or organization having rights in the invention must file separate statements as to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person concern, or organization having any rights in the invention is listed below:
☒ No such persons, concerns, or organizations exist.
☐ each such person, concerns, or organization is listed below:

Separate statements are required from each named person, concern, or organization having rights to the invention stating their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

NAME OF PERSON SIGNING Lance K. Ishimoto

TITLE OF PERSON IF OTHER THAN OWNER Vice President - Intellectual Property

ADDRESS OF PERSON SIGNING 4000 Research Forest Drive, The Woodlands, TX 77381

SIGNATURE ______________ DATE September 27, 2000
Reg. No. 41,866

NOVEL HUMAN KINASE PROTEINS AND POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S. Provisional Application Number 60/156,511 which was filed on September 28, 1999 and is herein incorporated by reference in its entirety.

1. INTRODUCTION

The present invention relates to the discovery, identification, and characterization of novel human polynucleotides encoding proteins that share sequence similarity with animal kinases. The invention encompasses the described polynucleotides, host cell expression systems, the encoded proteins, fusion proteins, polypeptides and peptides, antibodies to the encoded proteins and peptides, and genetically engineered animals that either lack or over express the disclosed genes, antagonists and agonists of the proteins, and other compounds that modulate the expression or activity of the proteins encoded by the disclosed genes that can be used for diagnosis, drug screening, clinical trial monitoring and the treatment of physiological disorders.

2. BACKGROUND OF THE INVENTION

Kinases mediate phosphorylation of a wide variety of proteins and compounds in the cell. Along with phosphatases, kinases are involved in a wide range of regulatory pathways. Given the physiological importance of kinases, they have been subject to intense scrutiny and are proven drug targets.

3. SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification, and characterization of nucleotides that encode novel human proteins, and the corresponding amino acid sequences

of these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with animal kinases, and more particularly serine/threonine protein kinases. As such, the novel sequences represent a new family of proteins having homologues and orthologs across a range of phyla and species.

The novel human nucleic acid sequences described herein, encode alternative proteins/open reading frames (ORFs) of 187, 356, 324, 198, 347, and 315 amino acids in length (see SEQ ID NOS: 2, 4, 6, 8, 10, and 12).

The invention also encompasses agonists and antagonists of the described NHPs, including small molecules, large molecules, mutant NHPs, or portions thereof that compete with native NHP, peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (*e.g.*, antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the described NHP sequences (*e.g.*, expression constructs that place the described gene under the control of a strong promoter system). The present invention also includes both transgenic animals that express a NHP transgene, and NHP "knock-outs" (which can be conditional) that do not express a functional NHP.

Further, the present invention also relates to processes for identifying compounds that modulate, *i.e.*, act as agonists or antagonists, of NHP expression and/or NHP product activity that utilize purified preparations of the described NHPs and/or NHP product, or cells expressing the same. Such compounds can be used as therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders or imbalances.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequence of novel human ORFs that encode the described NHP kinase-like proteins.

5. DETAILED DESCRIPTION OF THE INVENTION

The NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia,* human cell lines, and human brain, pituitary, spinal cord, spleen, trachea, kidney, prostate, testis, and adrenal gland cells. The described sequences were compiled from gene trapped cDNAs, and human testis cDNA libraries, (Clontech, Palo Alto, CA).

The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of the NHPs that correspond to functional domains, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence in deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of an NHP, or one of its domains (*e.g.*, a receptor/ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the described polynucleotides such as oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or

gene therapy constructs comprising a sequence first disclosed in the Sequence Listing.

As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF) that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, *e.g.*, hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of the DNA sequence that encode and express an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, *e.g.*, washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encode a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding NHP ORFs, or their functional equivalents, encoded by polynucleotide sequences that are about 99, 95, 90, or about 85 percent similar to corresponding regions of SEQ ID NO:1 (as measured by BLAST sequence comparison analysis using, for example, the GCG sequence analysis package using default parameters).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length may partially overlap each other and/or the NHP sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described NHP polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 18, and preferably about 25, nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences may begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

For oligonucleotide probes, highly stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP sequence antisense molecules, useful, for example, in NHP sequence regulation (for and/or as antisense primers in amplification reactions of NHP gene nucleic acid sequences). With respect to NHP sequence regulation, such techniques can be used to regulate biological functions. Further, such sequences can be used as part of ribozyme and/or triple helix sequences that are also useful for NHP sequence regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. *16*:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual (and

periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP sequence homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or "wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from, for example, human or non-human cell lines or tissue, such as prostate, rectum, colon, or adrenal gland, known or suspected to express an allele of a NHP gene. The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (*i.e.*, one known, or suspected, to express a NHP sequence, such as, for example, testis tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5′ end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*.

A cDNA encoding a mutant NHP sequence can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5′ end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP sequence product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (*e.g.*, a person manifesting a NHP-associated phenotype such as, for example, immune disorders, obesity, high

blood pressure, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP sequence, or any suitable fragment thereof, can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele. In this manner, gene products made by the putatively mutant tissue may be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against a normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.)

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frameshift mutation), polyclonal antibodies to a NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

An additional application of the described novel human polynucleotide sequences is their use in the molecular mutagenesis/evolution of proteins that are at least partially encoded by the described novel sequences using,

for example, polynucleotide shuffling or related methodologies. Such approaches are described in U.S. Patents Nos. 5,830,721 and 5,837,458 which are herein incorporated by reference in their entirety.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements (*i.e.*, antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP sequence under the control of an exogenously introduced regulatory element (*i.e.*, gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include, but are not limited to, the human cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters) the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast α-mating factors.

Where, as in the present instance, some of the described NHP peptides or polypeptides are thought to be cytoplasmic proteins, expression systems can be engineered that produce soluble derivatives of a NHP (corresponding to a NHP extracellular and/or

intracellular domains, or truncated polypeptides lacking one or more hydrophobic domains) and/or NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP domain to an IgFc), NHP antibodies, and anti-idiotypic antibodies (including Fab fragments) that can be used in therapeutic applications. Preferably, the above expression systems are engineered to allow the desired peptide or polypeptide to be recovered from the culture media.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of the NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP sequence (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (*e.g.*, expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of NHP in the body. The use of engineered host cells and/or animals can offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor/ligand of a NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding the NHPs, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP or a protein interactive therewith. Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo*; these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHPs, mutant NHPs, as well as antisense and ribozyme molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating biological disorders.

Various aspects of the invention are described in greater detail in the subsections below.

5.1 THE NHP SEQUENCES

The cDNA sequences and the corresponding deduced amino acid sequences of the described NHPs are presented in the Sequence Listing. The NHP nucleotide sequences were obtained from human cDNA libraries using probes and/or primers generated from human gene trapped sequence tags.

Expression analysis has provided evidence that the described NHPs can be expressed in human tissues as well as gene trapped

human cells. In addition to the serine/threonine kinases, the described NHPs also share significant similarity to a range of additional kinase families such as cell division protein kinases, cyclin dependent kinase, etc. from a range of phyla and species. Given the physiological importance of protein kinases, they have been subject to intense scrutiny as exemplified and discussed in U.S. Patent No. 5,817,479 herein incorporated by reference in its entirety.

During the generation of the described sequences, a polymorphism was identified in the 3' UTR reported in SEQ ID NO:13 (which includes a complete NHP ORF flanked by 5' and 3' sequences.

5.2 NHPS AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in diagnostic assays, for the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and disease.

The Sequence Listing discloses the amino acid sequences encoded by the described NHP sequences. The NHPs have initiator methionines in DNA sequence contexts consistent with eucaryotic translation initiation sites.

The NHP amino acid sequences of the invention include the amino acid sequence presented in the Sequence Listing as well as analogues and derivatives thereof. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP protein encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any

novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (*e.g.*, proteolytic activity, ion flux, tyrosine phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and

glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where the NHP peptide or polypeptide can exist, or has been engineered to exist, as a soluble or secreted molecule, the soluble NHP peptide or polypeptide can be recovered from the culture media. Such expression systems also encompass engineered host cells that express a NHP, or functional equivalent, *in situ*. Purification or enrichment of a NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that may be used for purposes of the invention include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian

viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which a NHP coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. A NHP coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*, virus lacking the

proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda cells in which the inserted sequence is expressed (*e.g.*, see Smith *et al.*, 1983, J. Virol. 46: 584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric sequence may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also be required for efficient translation of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP sequence or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (See Bittner *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the NHP product. Such engineered cell

lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, 1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, 1984, Gene *30*:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, Proc. Natl. Acad. Sci. USA *88*:8972-8976). In this system, the sequence of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP sequence product. Additionally, such antibodies can be used in conjunction gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with the NHP, an NHP peptide (*e.g.*, one corresponding the a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not

limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet hemocyanin, tetanus toxoid, diptheria toxoid, ovalbumin, cholera toxoid or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated in vitro or in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci., *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate

biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *334*:544-546) can be adapted to produce single chain antibodies against NHP sequence products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science, *246*:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor/ligand can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind, activate, or neutralize a NHP, NHP receptor, or NHP ligand. Such anti-idiotypic

antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP mediated pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP polynucleotide described in SEQ ID NO: 9.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 10; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 9 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:12.

ABSTRACT

Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	ATTORNEY DOCKET NO. LEX-0046-USA

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Novel Human Kinase Proteins and Polynucleotides Encoding the Same

the specification of which is attached hereto unless the following box is checked:

( ) was filed on _______________ as US Application Serial No. or PCT International Application Number _________________ and was amended on _________________ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			YES:____ NO:____
			YES:____ NO:____

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE
60/156,511	9/28/1999

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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aacttcatga aggggtgtct gaagatgaat ccagatgaca gattaacctg ttcccaactc 840

ctggagagct cctactttga ttcttttcaa gaggcccaaa ttaaaagaaa agcacgtaat 900
gaaggaagaa acagaagacg ccaacaggtc agaggctgtg tttggctgct gcagctctgc 960
tccaggctgc at 972

<210> 6
<211> 324
<212> PRT
<213> homo sapiens

<400> 6
Met Glu Lys Tyr Glu Lys Leu Ala Lys Thr Gly Glu Gly Ser Tyr Gly
1 5 10 15
Val Val Phe Lys Cys Arg Asn Lys Thr Ser Gly Gln Val Val Ala Val
20 25 30
Lys Lys Phe Val Glu Ser Glu Asp Asp Pro Val Val Lys Lys Ile Ala
35 40 45
Leu Arg Glu Ile Arg Met Leu Lys Gln Leu Lys His Pro Asn Leu Val
50 55 60
Asn Leu Ile Glu Val Phe Arg Arg Lys Arg Lys Met His Leu Val Phe
65 70 75 80
Glu Tyr Cys Asp His Thr Leu Leu Asn Glu Leu Glu Arg Asn Pro Asn
85 90 95
Gly Val Ala Asp Gly Val Ile Lys Ser Val Leu Trp Gln Thr Leu Gln
100 105 110
Ala Leu Asn Phe Cys His Ile His Asn Cys Ile His Arg Asp Ile Lys
115 120 125
Pro Glu Asn Ile Leu Ile Thr Lys Gln Gly Ile Ile Lys Ile Cys Asp
130 135 140
Phe Gly Phe Ala Gln Ile Leu Ile Pro Gly Asp Ala Tyr Thr Asp Tyr
145 150 155 160
Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Leu Leu Val Gly Asp Thr
165 170 175
Gln Tyr Gly Ser Ser Val Asp Ile Trp Ala Ile Gly Cys Val Phe Ala
180 185 190
Glu Leu Leu Thr Gly Gln Pro Leu Trp Pro Gly Lys Ser Asp Val Asp
195 200 205
Gln Leu Tyr Leu Ile Ile Arg Thr Leu Gly Lys Leu Ile Pro Arg His
210 215 220
Gln Ser Ile Phe Lys Ser Asn Gly Phe Phe His Gly Ile Ser Ile Pro
225 230 235 240
Glu Pro Glu Asp Met Glu Thr Leu Glu Glu Lys Phe Ser Asp Val His
245 250 255
Pro Val Ala Leu Asn Phe Met Lys Gly Cys Leu Lys Met Asn Pro Asp
260 265 270
Asp Arg Leu Thr Cys Ser Gln Leu Leu Glu Ser Ser Tyr Phe Asp Ser
275 280 285
Phe Gln Glu Ala Gln Ile Lys Arg Lys Ala Arg Asn Glu Gly Arg Asn
290 295 300
Arg Arg Arg Gln Gln Val Arg Gly Cys Val Trp Leu Leu Gln Leu Cys
305 310 315 320
Ser Arg Leu His

<210> 7
<211> 594
<212> DNA

<213> homo sapiens

<400> 7
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gatcctgttg ttaagaaaat agcactaaga gaaatacgta tgttgaagca attaaaacat 180
ccaaatcttg tgaacctcat cgaggtgttc aggagaaaaa ggaaaatgca tttagttttt 240
gaatactgtg atcatacact tttaaatgag ctggaaagaa acccaaatgg agttgctgat 300
ggagtgatca aaagcgtatt atggcaaaca cttcaagctc ttaatttctg tcatatacat 360
aactgtattc acagagatat aaaacctgaa aatattctaa taactaagca aggaataatc 420
aagatttgtg acttcgggtt tgcacaaatt ctgagttgga cttcatcttt ctctggtgcc 480
tccttgattg gcttaatagt tgaccttctg aattcttttt ctgccaattc agagattttt 540
ctcctggctt ggatccattg ctggaaaatt aatcccaaga catcaatcaa tctt 594

<210> 8
<211> 198
<212> PRT
<213> homo sapiens

<400> 8
Met Glu Lys Tyr Glu Lys Leu Ala Lys Thr Gly Glu Gly Ser Tyr Gly
1   5   10   15
Val Val Phe Lys Cys Arg Asn Lys Thr Ser Gly Gln Val Val Ala Val
            20   25   30
Lys Lys Phe Val Glu Ser Glu Asp Asp Pro Val Val Lys Lys Ile Ala
        35   40   45
Leu Arg Glu Ile Arg Met Leu Lys Gln Leu Lys His Pro Asn Leu Val
    50   55   60
Asn Leu Ile Glu Val Phe Arg Arg Lys Arg Lys Met His Leu Val Phe
65   70   75   80
Glu Tyr Cys Asp His Thr Leu Leu Asn Glu Leu Glu Arg Asn Pro Asn
                85   90   95
Gly Val Ala Asp Gly Val Ile Lys Ser Val Leu Trp Gln Thr Leu Gln
            100   105   110
Ala Leu Asn Phe Cys His Ile His Asn Cys Ile His Arg Asp Ile Lys
        115   120   125
Pro Glu Asn Ile Leu Ile Thr Lys Gln Gly Ile Ile Lys Ile Cys Asp
    130   135   140
Phe Gly Phe Ala Gln Ile Leu Ser Trp Thr Ser Ser Phe Ser Gly Ala
145   150   155   160
Ser Leu Ile Gly Leu Ile Val Asp Leu Leu Asn Ser Phe Ser Ala Asn
                165   170   175
Ser Glu Ile Phe Leu Leu Ala Trp Ile His Cys Trp Lys Ile Asn Pro
            180   185   190
Lys Thr Ser Ile Asn Leu
        195

<210> 9
<211> 1041
<212> DNA
<213> homo sapiens

<400> 9
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gatcctgttg ttaagaaaat agcactaaga gaaatacgta tgttgaagca attaaaacat 180

ccaaatcttg tgaacctcat cgaggtgttc aggagaaaaa ggaaaatgca tttagttttt 240
gaatactgtg atcatacact tttaaatgag ctggaaagaa acccaaatgg agttgctgat 300
ggagtgatca aaagcgtatt atggcaaaca cttcaagctc ttaatttctg tcatatacat 360
aactgtattc acagagatat aaaacctgaa aatattctaa taactaagca aggaataatc 420
aagatttgtg acttcgggtt tgcacaaatt ctgattccag gagatgccta caccgattat 480
gtagctacga gatggtaccg agctcctgaa cttcttgtgg gagatactca gtatggttct 540
tcagtcgata tatgggctat tggttgtgtt tttgcagagc tcctgacagg ccagccactg 600
tggcctggaa aatcagatgt ggaccaactt tatctgataa tcagaacact agtagagacg 660
gggtttcgcc atgttgacca ggctggtctc gaactcttga cgtcaagtga tccacctgcc 720
gtagcctctc aaagtgctgg aattacagga aaattaatcc caagacatca atcaatcttt 780
aaaagtaacg ggtttttcca tggcatcagt atacctgagc cagaagacat ggaaactctt 840
gaggaaaagt tctcagatgt tcatcctgtg gctctgaact tcatgaaggg gtgtctgaag 900
atgaatccag atgacagatt aacctgttcc caactcctgg agagctccta ctttgattct 960
tttcaagagg cccaaattaa aagaaaagca cgtaatgaag gaagaaacag aagacgccaa 1020
caggtacttc cgctcaaaag t 1041

<210> 10
<211> 347
<212> PRT
<213> homo sapiens

<400> 10
Met Glu Lys Tyr Glu Lys Leu Ala Lys Thr Gly Glu Gly Ser Tyr Gly
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Val Val Phe Lys Cys Arg Asn Lys Thr Ser Gly Gln Val Val Ala Val
20 25 30
Lys Lys Phe Val Glu Ser Glu Asp Asp Pro Val Val Lys Lys Ile Ala
35 40 45
Leu Arg Glu Ile Arg Met Leu Lys Gln Leu Lys His Pro Asn Leu Val
50 55 60
Asn Leu Ile Glu Val Phe Arg Arg Lys Arg Lys Met His Leu Val Phe
65 70 75 80
Glu Tyr Cys Asp His Thr Leu Leu Asn Glu Leu Glu Arg Asn Pro Asn
85 90 95
Gly Val Ala Asp Gly Val Ile Lys Ser Val Leu Trp Gln Thr Leu Gln
100 105 110
Ala Leu Asn Phe Cys His Ile His Asn Cys Ile His Arg Asp Ile Lys
115 120 125
Pro Glu Asn Ile Leu Ile Thr Lys Gln Gly Ile Ile Lys Ile Cys Asp
130 135 140
Phe Gly Phe Ala Gln Ile Leu Ile Pro Gly Asp Ala Tyr Thr Asp Tyr
145 150 155 160
Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Leu Leu Val Gly Asp Thr
165 170 175
Gln Tyr Gly Ser Ser Val Asp Ile Trp Ala Ile Gly Cys Val Phe Ala
180 185 190
Glu Leu Leu Thr Gly Gln Pro Leu Trp Pro Gly Lys Ser Asp Val Asp
195 200 205
Gln Leu Tyr Leu Ile Ile Arg Thr Leu Val Glu Thr Gly Phe Arg His
210 215 220
Val Asp Gln Ala Gly Leu Glu Leu Leu Thr Ser Ser Asp Pro Pro Ala
225 230 235 240
Val Ala Ser Gln Ser Ala Gly Ile Thr Gly Lys Leu Ile Pro Arg His
245 250 255
Gln Ser Ile Phe Lys Ser Asn Gly Phe Phe His Gly Ile Ser Ile Pro
260 265 270

Glu Pro Glu Asp Met Glu Thr Leu Glu Glu Lys Phe Ser Asp Val His
275 280 285
Pro Val Ala Leu Asn Phe Met Lys Gly Cys Leu Lys Met Asn Pro Asp
290 295 300
Asp Arg Leu Thr Cys Ser Gln Leu Leu Glu Ser Ser Tyr Phe Asp Ser
305 310 315 320
Phe Gln Glu Ala Gln Ile Lys Arg Lys Ala Arg Asn Glu Gly Arg Asn
325 330 335
Arg Arg Arg Gln Gln Val Leu Pro Leu Lys Ser
340 345

<210> 11
<211> 945
<212> DNA
<213> homo sapiens

<400> 11
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gatcctgttg ttaagaaaat agcactaaga gaaatacgta tgttgaagca attaaaacat 180
ccaaatcttg tgaacctcat cgaggtgttc aggagaaaaa ggaaaatgca tttagttttt 240
gaatactgtg atcatacact tttaaatgag ctggaaagaa acccaaatgg agttgctgat 300
ggagtgatca aaagcgtatt atggcaaaca cttcaagctc ttaatttctg tcatatacat 360
aactgtattc acagagatat aaaacctgaa aatattctaa taactaagca aggaataatc 420
aagatttgtg acttcgggtt tgcacaaatt ctgattccag gagatgccta caccgattat 480
gtagctacga gatggtaccg agctcctgaa cttcttgtgg gagatactca gtatggttct 540
tcagtcgata tatgggctat tggttgtgtt tttgcagagc tcctgacagg ccagccactg 600
tggcctggaa aatcagatgt ggaccaactt tatctgataa tcagaacact aggaaaatta 660
atcccaagac atcaatcaat ctttaaaagt aacgggtttt tccatggcat cagtatacct 720
gagccagaag acatggaaac tcttgaggaa aagttctcag atgttcatcc tgtggctctg 780
aacttcatga aggggtgtct gaagatgaat ccagatgaca gattaacctg ttcccaactc 840
ctggagagct cctactttga ttcttttcaa gaggcccaaa ttaaaagaaa agcacgtaat 900
gaaggaagaa acagaagacg ccaacaggta cttccgctca aaagt 945

<210> 12
<211> 315
<212> PRT
<213> homo sapiens

<400> 12
Met Glu Lys Tyr Glu Lys Leu Ala Lys Thr Gly Glu Gly Ser Tyr Gly
1 5 10 15
Val Val Phe Lys Cys Arg Asn Lys Thr Ser Gly Gln Val Val Ala Val
20 25 30
Lys Lys Phe Val Glu Ser Glu Asp Asp Pro Val Val Lys Lys Ile Ala
35 40 45
Leu Arg Glu Ile Arg Met Leu Lys Gln Leu Lys His Pro Asn Leu Val
50 55 60
Asn Leu Ile Glu Val Phe Arg Arg Lys Arg Lys Met His Leu Val Phe
65 70 75 80
Glu Tyr Cys Asp His Thr Leu Leu Asn Glu Leu Glu Arg Asn Pro Asn
85 90 95
Gly Val Ala Asp Gly Val Ile Lys Ser Val Leu Trp Gln Thr Leu Gln
100 105 110
Ala Leu Asn Phe Cys His Ile His Asn Cys Ile His Arg Asp Ile Lys
115 120 125

Pro Glu Asn Ile Leu Ile Thr Lys Gln Gly Ile Ile Lys Ile Cys Asp
    130   135   140
Phe Gly Phe Ala Gln Ile Leu Ile Pro Gly Asp Ala Tyr Thr Asp Tyr
145   150   155   160
Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Leu Leu Val Gly Asp Thr
                165   170   175
Gln Tyr Gly Ser Ser Val Asp Ile Trp Ala Ile Gly Cys Val Phe Ala
            180   185   190
Glu Leu Leu Thr Gly Gln Pro Leu Trp Pro Gly Lys Ser Asp Val Asp
        195   200   205
Gln Leu Tyr Leu Ile Ile Arg Thr Leu Gly Lys Leu Ile Pro Arg His
    210   215   220
Gln Ser Ile Phe Lys Ser Asn Gly Phe Phe His Gly Ile Ser Ile Pro
225   230   235   240
Glu Pro Glu Asp Met Glu Thr Leu Glu Glu Lys Phe Ser Asp Val His
                245   250   255
Pro Val Ala Leu Asn Phe Met Lys Gly Cys Leu Lys Met Asn Pro Asp
            260   265   270
Asp Arg Leu Thr Cys Ser Gln Leu Leu Glu Ser Ser Tyr Phe Asp Ser
        275   280   285
Phe Gln Glu Ala Gln Ile Lys Arg Lys Ala Arg Asn Glu Gly Arg Asn
    290   295   300
Arg Arg Arg Gln Gln Val Leu Pro Leu Lys Ser
305   310   315

<210> 13
<211> 1819
<212> DNA
<213> homo sapiens

<400> 13
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caccgtcgcc ctgtgggtgc agtgcagcat tgtactgcaa gtcaatcgat acaataattt 120
aagtcacttc agctataatg gaaaagtatg aaaaattagc taagactgga gaagggtctt 180
atggggttgt attcaaatgc agaaacaaaa cctctggaca agtagtagct gttaaaaaat 240
ttgtggaatc tgaagatgat cctgttgtta agaaaatagc actaagagaa atacgtatgt 300
tgaagcaatt aaaacatcca aatcttgtga acctcatcga ggtgttcagg agaaaaagga 360
aaatgcattt agtttttgaa tactgtgatc atacactttt aaatgagctg gaaagaaacc 420
caaatggagt tgctgatgga gtgatcaaaa gcgtattatg gcaaacactt caagctctta 480
atttctgtca tatacataac tgtattcaca gagatataaa acctgaaaat attctaataa 540
ctaagcaagg aataatcaag atttgtgact tcgggtttgc acaaattctg agttggactt 600
catctttctc tggtgcctcc ttgattggct taatagttga ccttctgaat tctttttctg 660
ccaattcaga gatttttctc ctggcttgga tccattgctg acacagtgtt tcaccatggg 720
gcccaggctc atctcgaact tctggcctca agtgatcctt ccacctcggc ctcccaaagt 780
gctggattgc aagtgtgagc caccgtgccc agccagattt ttcaaacaat aactactgag 840
agctcacaag attgttttta gtgggaacac aatttcgaac aaattcttga gaacgcattc 900
caggagatgc ctacaccgat tatgtagcta cgagatggta ccgagctcct gaacttcttg 960
tgggagatac tcagtatggt tcttcagtcg atatatgggc tattggttgt gtttttgcag 1020
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taatcagaac actagtagag acggggtttc gccatgttga ccaggctggt ctcgaactct 1140
tgacgtcaag tgatccacct gccgtagcct ctcaaagtgc tggaattaca ggaaaattaa 1200
tcccaagaca tcaatcaatc tttaaaagta acgggttttt ccatggcatc agtatacctg 1260
agccagaaga catggaaact cttgaggaaa agttctcaga tgttcatcct gtggctctga 1320
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tggagagctc ctactttgat tcttttcaag aggcccaaat taaaagaaaa gcacgtaatg 1440
aaggaagaaa cagaagacgc caacaggtca gaggctgtgt ttggctgctg cagctctgct 1500

ccaggctgca ttgagaatcg atttcgagtg tcttctcatt cagggaccca gccaaggagc 1560
agctcatatg ggaaatatgc ccttctcatg gcagaggccc gaacttgaat acctaatgtc 1620
tgtcaggagt gacttccgct caaaagttaa agtgctataa aaataattcc ttttttgttt 1680
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tgtagtgatt gctagcttaa taaatattgg gaattgatgt ataaaaccct agactatgaa 1800
aatatcaaaa aaaaaaaaa 1819